MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 2, 2005

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THROUGH: Mark Avigan, M.D., C.M., Director
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TO: Solomon Iyasu, MD, MPH., Team Leader
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Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review (PID# D040211)
Sodium ferric gluconate complex (Ferrlecit) NDA# 20-955
Pediatric Exclusivity Approval Date: March 24, 2004

Executive Summary

As requested by the Office of Counter-Terrorism and Pediatrics, we reviewed the pediatric adverse events in association with the use of sodium ferric gluconate (Ferrlecit) in children aged 16 years and younger. The time period of interest was the one-year period (the search period is expanded to 13 months to allow for the time lag needed to collect 12 months of data) following FDA Pediatric Exclusivity approval, March 24, 2004 through April 24, 2005.

For the 12-month time period after pediatric exclusivity was granted, we identified two labeled adverse events of irritability and respiratory distress for a 4-month-old boy who was given sodium ferric gluconate (Ferrlecit) and immune globulin (Polygam). The patient was hospitalized in the ICU; outcome was provided. We will continue to monitor adverse events for a second year because one case is insufficient to conduct a meaningful analysis.

AERS Search Results: Sodium ferric gluconate (Ferrlecit)

AERS Search Dates: Searches for U.S. and foreign cases during the following time periods, (1) February 18, 1999 (approval date) to April 24, 2005, and (2) March 24, 2004 (pediatric exclusivity date) to April 24, 2005.

A. Adverse events from marketing approval date, February 18, 1999 to April 24, 2005:

1. Raw counts of reports: Table 1 (parentheses denote U.S. origin report counts)

	All reports (US)	Serious (US)	Death (US)
All ages	181 (169)	137 (125)	10 (1)
Adults (≥17)	157 (146)	119 (108)	8 (7)
Peds (0-16)	4 (4)	4 (4)	0 (0)

Figure 1: Reporting trend for pediatric reports from approval date:

Year	Report count
2000	1
2001	1
2003	1
2004	1

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups (underscore denotes unlabeled events).

   All ages: Hypotension (40), vomiting (34), nausea (31), dyspnoea (25), abdominal pain (19), diarrhea (19), hyperhidrosis (19), dizziness (17), blood pressure decreased (16), chest pain (14), paraesthesia (14), urticaria (13), oedema peripheral (12), asthenia (11), back pain (10), erythema (10), flushing (10), anaphylactic reaction (9), chills (9), medication error (9)

   Adults: Hypotension (38), vomiting (32), nausea (28), dyspnoea (22), diarrhea (19), hyperhidrosis (18), dizziness (16), abdominal pain (15), blood pressure decreased (14), chest pain (13), urticaria (13), oedema peripheral (12), paraesthesia (12), asthenia (10), flushing (10), erythema (9), syncope (9), anaphylactic reaction (8), back pain (8), burning sensation (8)

   Peds: Abdominal pain (1), grand mal convulsion (1), headache (1), irritability (1), nausea (1), paraesthesia (1), respiratory distress (1), retching (1)

B. From Pediatric Exclusivity approval date (March 24, 2004) through AERS data cut-off date (April 24, 2005):

1. Raw counts of reports: Table 2

	All reports (US)	Serious (US)	Death (US)
All ages	36 (31)	22 (28)	2 (1)
Adults (≥17)	30 (26)	27 (23)	2 (1)
Peds (0-16)	1 (1)	1 (1)	0 (0)

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups including identifying events not previously described in the label.

   All ages: Hypotension (9), vomiting (7), dyspnoea (5), paraesthesia (5), diarrhea (4), dizziness (4), erythema (4), infusion related reaction (4), nausea (4), abdominal pain (3), arthralgia (3), asthenia (3), burning sensation (3), cardiac arrest (3), chills (3), hyperhidrosis (3), loss of consciousness (3), muscle spasms (3), respiratory distress (3), swelling face (3)

   Adults: Hypotension (8), vomiting (6), diarrhea (4), dizziness (4), dyspnoea (4), infusion related reaction (4), nausea (4), paraesthesia (4), arthralgia (3), burning sensation (3), erythema (3), loss of consciousness (3), muscle spasms (3), swelling face (3), tachycardia (3), urticaria (3), abdominal pain (2), asthenia (2), cardiac arrest (2), chest pain (2)

   Peds: Respiratory distress (1), irritability (1)

Postmarketing hands-on review of all peds adverse event reports from all sources received during the one-year after a drug receives pediatric market exclusivity.

There was one report (FDA# 5667524) of irritability and respiratory distress in a 4-month-old boy that was submitted during this time period. The patient received 3.5 grams of Polygam (immune globulin intravenous [human]) and 15 mg of Ferrlecit as a one-time dose; he had been premedicated with diphenhydramine and acetaminophen. He was stable during the infusion, but was slightly fussy with normal O2 saturation post infusion. He was discharged to his renal clinic appointment the same day where he had significant respiratory distress and was "disky." He was treated with hydrocortisone, diphenhydramine, and albuterol without success. The patient was taken to the ER and given subcutaneous epinephrine without improvement; he was intubated and admitted to ICU. His medical history included end-stage renal disease secondary to adult autosomal dominant polycystic kidney disease and status post bilateral nephrectomy; he is peritoneal dialysis dependent.

Summary

For the 12-month time period after pediatric exclusivity was granted, we identified two labeled adverse events of irritability and respiratory distress for a 4-month-old boy who was given sodium ferric gluconate (Ferrlecit) and immune globulin (Polygam). The patient was hospitalized in the ICU; outcome was provided. We will continue to monitor adverse events for a second year because one case is insufficient to conduct a meaningful analysis.

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Concur:

Lanh Green 5/2/05

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Appendix

Standard Searches:

A. Adults (17 yrs and above)
   1. All outcomes from AP date (no set criteria)
   2. Serious outcomes from AP date
   3. Death as an outcome from AP date
   4. All outcomes from PE date to present or any desired date
   5. Serious outcomes from PE date to present or any desired date
   6. Death as an outcome from PE date to present or any desired date

B. Ages 0-16 yrs ONLY
   1. Same as above 1-6
   2. Retrieve case reports for hands-on review

Standard Printouts for Attachments:

A. Adults (17 yrs and above)
   1. Frequency counts of all preferred terms (PT) in cases
   2. Frequency counts of all PT in cases with serious outcomes
   3. Frequency counts of all PT in cases with death as an outcome
   4. Frequency counts of cases by Gender and ages

B. Ages 0-16 yrs ONLY
   Same as above 1-4

Drug Product Information

Limitations of the Adverse Event Reporting System (AERS)

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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/s/

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5/10/05 10:41:50 AM
PHARMACIST

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DRUG SAFETY OFFICE REVIEWER